Reviewer's report

Title: Lessons and implications from a mass immunization campaign in squatter settlements of Karachi, Pakistan: an experience from a cluster-randomized double-blinded controlled trial
[NCT00125047]

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Reviewer: Christian Gluud

Reviewer's report:

General

Mohammad Imran Khan and colleagues describe in the manuscript the logistics, the feasibility, and some safety aspects of a cluster randomised trial conducted in squatter settlements of Karachi, Pakistan. In the clusters, the investigators compare ‘Vi’ typhoid polysaccharide vaccine (experimental intervention) versus hepatitis A vaccine (control intervention). The trial is part of the Diseases of the Most Impoverished (DOMI) typhoid fever programme started in 2001, a prestigious project having received substantial funding from several important sources. Starting such a trial must have demanded lots of energy and skills. Most of the text reads well and I guess I have a good impression of the complexities the investigators had to overcome to reach this far. I have a number of comments that I suggest the authors’ address.

The trial has been registered – but I lacked relevant information on this trial at the trial register.

- Major Revisions

1. The interest in assessing the experimental intervention would benefit in clarity from having a systemic review backing the complexity in deciding to use the intervention. How many trials have been conducted with this vaccine versus placebo? What are their findings with relative risks and 95% confidence intervals on which outcomes? How many trials have been conducted with this vaccine versus other vaccines for typhoid fever? What are their findings with relative risks and 95% confidence intervals? I suggest that the authors identify such systematic reviews or conduct them themselves.

2. Why was this ‘Vi’ vaccine chosen and not a more long-term effective ‘Vi’ vaccine?

3. The relevance in assessing the experimental intervention versus the control intervention would similarly benefit in clarity from having a systemic review backing the deciding for using this control intervention. How many trials have been conducted with this hepatitis A vaccine versus placebo? What are their findings with relative risks and 95% confidence intervals? How many trials have been conducted with this vaccine versus other vaccines for hepatitis A? What are their findings with relative risks and 95% confidence intervals? I suggest that the authors identify such systematic reviews or conduct them themselves.

4. What is the chance that hepatitis A vaccination would offer any benefit in this population? I suspect that the chance of any beneficial effect – due to the fact that a high proportion of children already has been exposed to hepatitis A – is close to negligible?

5. This trial was approved by a number of ethical committees from several organisations/countries. It
is s not fully clear to me why this has happened. I suggest that the authors give a detailed description of the ethical considerations they have, eg, the description included in their protocol. In planning a clinical trial of a new intervention, two issues should be addressed. The first is the question of whether the use of the new intervention is justified. The second is the choice of the appropriate control group. Both issues are dependent on the knowledge about the therapeutic value of the treatments to be compared (see points 1-4 above). This is an important reason why clinical trials should be preceded by systematic reviews to assess the status of knowledge. The trial would not be justified if one of the treatments to be assessed is known to be superior to the other. A clinical trial is only justified if the participant and the clinician are not certain about which treatment to choose from the available options. If they are uncertain (indifferent) about the relative value of the treatments, it is time for a trial. This is not only because the trial will help resolve this uncertainty but also because it is the fairest way to choose the preventive strategy.

6. Following the same logic, I would also like to see described in more detail what was the information (written and verbal) given to the a) community leaders, b) the parents, c) the guardians, as well as d) the participants on benefits and harm of experimental and control interventions.

7. How was the sample size of this trial calculated. In a ‘sister’ (or aunt?) publication (Acosta et al, Tropical Medicine and International Health 2005;10:1219-1228) we learn that 60 clusters with 30,000 participants was the goal of this trial, - but neither in this publication, nor the present manuscript, nor at the NCT-registration site do I find description of the sample size calculation.

8. We now learn that about 21,059 children lived in the 60 clusters, but only 12,830 were randomised. This represents only 43% of the target. This aspect needs to be discussed including an assessment of the impact on the potential conclusions top be drawn.

9. The authors should report the trial and the flow of patients according to instructions in the CONSORT Statement/CONSORT diagram.

10. What was the role of the pharmaceutical sponsor in designing this trial?

11. What was the role of the pharmaceutical sponsor in reporting this trial?

12. What are the risks of breaking the code in the trial due to the use of similar code letters in the two groups of clusters? Would the investigators do the same if they were to plan the trial today?

13. Maybe the reporting of adverse events should await breaking of the code, so that beneficial and harmful effects can be assessed in the same report. Accordingly, the present publication could focus on justification of the trial as well as design and feasibility issues.

14. As this manuscript deals with feasibility why not give the data on resource use for immunisation mentioned op p.15?

15. There was a significant migration between the clusters. How were the expectations during the planning of the trial regarding migration? What are the consequences for this cluster randomised trial of the observed substantial migration? How are the authors planning to deal with this problem during data analysis?

- Minor Essential Revisions

16. All randomised trials are of course controlled, so please do not use the pleonasm ‘randomised, double-blind controlled trial’ but rather ‘randomised, double-blind preventive trial’, which I think will be more descriptive.
17. On p.6 local EPI needs explanation first time.

18. On p.8 DSMB needs explanation first time it is used.

19. If reporting of adverse events stay in this manuscript, please consider: The reporting of adverse event will be wrong, because only a fraction of those vaccinated were checked for adverse events. Calculation of proportions (%) should use the correct denominator – and the total number with adverse events should be calculated based on extrapolation.

20. The three patients with serious adverse events ought to be described.

21. Tailored GCP – what is meant by that?

22. The authors may be right that the number of refusers may be lower during a non-trial mass vaccination campaign – but why?

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.